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09/724,538	11/28/2000	Daniel D. Shoemaker	9301-123	7044

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NEW YORK, NY 100362711

EXAMINER

LU, FRANK WEI MIN

ART UNIT PAPER NUMBER

1634

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,538	SHOEMAKER ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 April 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4-34,36,45,46,86-90,157-181,183,212,213,263-267 and 280-292 is/are pending in the application.
- 4a) Of the above claim(s) 46,88,212,213,266 and 267 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4-34,36,45,86,87,89,90,157-181,183,263-265 and 280-292 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☒ The proposed drawing correction filed on 01 April 2003 is: a) ☒ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: |

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DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on April 11, 2003 has been entered. The claims pending in this application are claims 1, 4-34, 36, 45, 46, 86-90, 157-181, 183, 212, 213, 263-267, and 280-292. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on April 11, 2003.

Specification

2. The disclosure is objected to because of the following informalities: there is Figure 4c. However, there is no description for Figure 4c in the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 4-34, 36, 45, 86, 87, 89, 90, 157-181, 183, 263-265, and 280-292 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claims 1, 4-6, 11, 12, 89, 90, 158, and 159 are rejected as vague and indefinite in view of the phrase "individual multiexons" because it is unclear what it intended. Since it is known that "multiexons" mean two or more exons and "individual" mean one or single subject, it is unclear

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what mean “individual multiexons” since two words “individual” and “multiexons” do not correspond each other. Please clarify.

6. Claims 36 and 183 are rejected as vague and indefinite in view of the phrase “wherein said expression levels are measured as absolute abundance” because it is unclear what it intended. Since absolute abundance is a relative number and only can be obtained by comparing two or more numbers, it is unclear how absolute abundance can be directly measured. Please clarify.

7. Claim 263 is rejected as vague and indefinite in view of the phrase “the longest variant of said exon having a plurality of different variants” because it is unclear what kind of variant of said exon having a plurality of different variants can be considered as the longest variant. Please clarify.

8. Claims 284 and 285 are rejected as vague and indefinite in view of the phrase “each of said variants being a form of said exon generated using a different splice junction of said exon” because it is unclear how each of said variant can be generated using a different splice junction of said exon. Does this phrase mean that each of said variant is generated on a splice junction of two adjacent exons? Please clarify.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

10. Claims 1, 4-7, and 45 are rejected under 35 U.S.C. 102(e) as being anticipated by DeRisi *et al.*, (Nature Genetics, 14, 457-460, 1996).

DeRisi *et al.*, teach use of cDNA microassay to analyze expression patterns in human cancer. They prepared fluorescence cDNA using mRNA from human tumorigenic UACC-903 and non-tumorigenic UACC-903(+6) by labeling with a green and red fluor respectively. These cDNAs was hybridized with an array including 870 different cDNAs and control. Several genes including TRP1/melanoma antigen gp 75 and WAF1 showed significant differences in expression between two cells (see pages 457 and 458).

Regarding claims 1, 4-7, and 45, since the phrase “wherein at least one gene in said plurality of different genes comprises an exon possibly having a plurality of different variants” indicates that said exon only has a possibility to have a plurality of different variants, said exon as recited in claim 1 can be read to not have a plurality of different variants, any limitation related to variants is not read into claim 1. Since multiexons is considered to have two or more exons and a

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cDNA often has two or more exons, a plurality of different multiexons are different cDNAs from different genes. Since several genes including TRP1/melanoma antigen gp 75 and WAF1 showed significant differences in expression between two cells, the method taught by DeRisi *et al.*, measures the expression levels of a plurality of different multiexons in each of a plurality of different genes in the genome of an organism (ie., human) from which said cell sample is derived as recited in claim 1.

Therefore, DeRisi *et al.*, teach all limitations recited in claims 1, 4-7, and 45.

Response to Arguments

In page 8, last paragraph bridging to page 9, first paragraph of applicant's remarks, applicant argues that: (1) "[D]eRisi does not teach measuring a *plurality of different individual exons or different individual multiexons* in each of a plurality of its genes." since "even through an mRNA transcribed from a gene may comprise more than one exon or may comprise a multiexon, measuring the expression level of the mRNA is not measuring a plurality of different individual exons or different individual multiexons in the gene."; and (2) "[D]eRisi also does not teach distinguishing among different variants of an exon so as to determine which variant(s) are expressed."

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, as shown in the rejection under 112, second paragraph, it is unclear what mean "individual multiexons". Second, since mRNA transcribed from a gene may comprise more than one exon or may comprise a multiexon, a plurality of different multiexons are different cDNAs from different genes. Since several genes including TRP1/melanoma antigen gp

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75 and WAF1 showed significant differences in expression between two cells, the method taught by DeRisi *et al.*, measures the expression levels of a plurality of different multiexons in each of a plurality of different genes in the genome of an organism (ie., human) from which said cell sample is derived as recited in claim 1. Third, the examiner agrees with applicant that “[D]eRisi also does not teach distinguishing among different variants of an exon so as to determine which variant(s) are expressed.”. Since the phrase “wherein at least one gene in said plurality of different genes comprises an exon possibly having a plurality of different variants” indicates that said exon only has a possibility to have a plurality of different variants and said exon as recited in claim 1 can be read to not have a plurality of different variants, any limitation related to variants is not read into claim 1.

11. Claims 1, 10-12, 22-26, 28-33, 45, 86, 87, 89, 90, 157-159, 169-173, 175-180, 265, and 280-282 are rejected under 35 U.S.C. 102(e) as being anticipated by Friend *et al.*, (US Patent No. 6,165,709, filed on February 26, 1998).

Regarding claims 1, 86, 89, and 90, Friend *et al.*, teach transcript arrays for analyzing the transcriptional state in a cell, and especially for comparing the transcriptional states of two cells wherein a first cell that was exposed to a drug and a second cell that was not drug-treated. cDNA from two different cells were labeled with different fluorescence dyes and hybridized with a microarray with immobilized nucleic acid probes. When the drug treatment had no effect, either directly or indirectly, on the relative abundance of a particular mRNA in a cell, the mRNA levels were equally prevalent in both cells. When the drug treatment had an effect, either directly or

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indirectly, on the relative abundance of a particular mRNA in a cell, the ratio of the first fluorescence dye to the second fluorescence dyes either increased or decreased (see columns 27-29 and 49-52). Since the phrase “wherein at least one gene in said plurality of different genes comprises an exon possibly having a plurality of different variants” indicates that said exon only has a possibility to have a plurality of different variants, said exon recited in claim 1 can be read to not have a plurality of different variants, any limitation related to variants is not read into claim 1. Since multiexons is considered to have two or more exons and a cDNA often has two or more exons, a plurality of different multiexons are different cDNAs from different genes. Since, when the drug treatment had no effect, either directly or indirectly, on the relative abundance of a particular mRNA in a cell, the mRNA levels were equally prevalent in both cells while, when the drug treatment had an effect, either directly or indirectly, on the relative abundance of a particular mRNA in a cell, the ratio of the first fluorescence dye to the second fluorescence dyes either increased or decreased, the method taught by Friend *et al.*, measures the expression levels of a plurality of different multiexons in each of a plurality of different genes in the genome of an organism (ie., human) from which said cell sample is derived as recited in claim 1.

Regarding claims 10, 157, 214, and 238, the binding sites of the microarray were DNA polynucleotides corresponding to at least a portion of each gene in an organism's genome. These DNAs were obtained by polymerase chain reaction (PCR) amplification of gene segments from genomic DNA, cDNA (e.g., by RT-PCR), or cloned sequences. For example, based on the known sequence of the genes or cDNA, chosen PCR primers were generated unique fragments (i.e. fragments that do not share more than 10 bases of contiguous identical sequence with any

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other fragment on the microarray) (see columns 29 and 30). An array immobilized these unique PCR fragments was considered as an array comprising a plurality of polynucleotide probes of different nucleotide sequences bound to different regions of a support wherein each of said different nucleotide sequences comprising a sequence complementary and hybridizable to a sequence in a multiexon. Here a multiexon was considered as a PCR product having two or more exons.

Regarding claims 11, 12, 158, and 159, it was known that some genes from yeast had at least 5 different exons.

Regarding claims 28-33, and 175-180, since claims 28-33 and 175-180 did not require that a sequence in the probe was fully complementary to a full length exon as recited in claims 30 and 177 or a multiexon as recited in claims 31 and 178 or a sequence spanning the splice junction between different exons as recited in claims 32 and 179, or sequence from adjacent exon as recited in claims 33 and 180, at least one nucleotide in these unique PCR fragments could hybridize to the sequence as recited in claims 30-33 and 177-180 and any size of sequence between any two complementary bases of the probe was considered as a linker as recited in claims 28 and 175 and any two complementary bases of the probe could be located in different exons as recited in claims 29 and 176 since unique PCR fragments were 300-800 bp (see column 50).

Regarding claims 22-26, 169-173, and 280-282, each gene fragment on the microarray was between about 50 bp and about 2000 bp, more typically between about 100 bp and about 1000 bp, and usually between about 300 bp and about 800 bp in length (see column 30, first paragraph).

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Regarding claims 45 and 87, the organism could be human (see column 37, last paragraph).

Regarding claim 265, a drug exposure to the cell was considered as a perturbation (see columns 27-29 and 49-52).

Therefore, Friend *et al.*, teach all limitations recited in claims 1, 10-12, 22-26, 28-33, 45, 86, 87, 89, 90, 157-159, 169-173, 175-180, 265, and 280-282.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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13. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeRisi *et al.*, (1998) as applied to claims 1, 4-7, and 45.

The teachings of DeRisi *et al.*, have been summarized previously, *supra*. DeRisi *et al.*, measured the expression levels of a plurality of different genes consisting of 870 different genes (see page 457, left column).

DeRisi *et al.*, did not disclose the limitations recited in claims 8 and 9.

However, in the absence of unexpected results, it would have been obvious to one having ordinary skill in the art at the time the invention was made to have measured the expression levels of 1000-10,000 different genes as recited in claims 8 and 9 in view of the reference of DeRisi *et al.*. One having ordinary skill in the art has been motivated to do so because optimization of numbers of measured different genes in a method for analyzing exon expression would have been obvious to one having ordinary skill in the art at the time the invention was made. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to measure the expression levels of 1000-10,000 different genes. Note that where the general conditions of a claim are disclosed in the prior art, it is not inventive, in the absence of an unexpected result, to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

14. Claims 27, 174, and 284 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friend *et al.*, (1998) as applied to claims 1, 10-12, 22-26, 28-33, 45, 86, 87, 89, 90, 157-159, 169-173, 175-180, 265, and 280-282.

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The teachings of Friend *et al.*, have been summarized previously, *supra*.

Friend *et al.*, did not disclose the limitations recited in claims 27, 174, and 284.

However, in the absence of unexpected results, it would have been obvious to one having ordinary skill in the art at the time the invention was made to have immobilized different length of polynucleotide probes on an array as recited in claims 27, 174, and 284 in view of patents of Friend *et al.*... One having ordinary skill in the art has been motivated to do so because optimization of the length of immobilized polynucleotide probes on an array would have been obvious to one having ordinary skill in the art at the time the invention was made. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to optimization of the length of immobilized polynucleotide probes on an array. Note that where the general conditions of a claim are disclosed in the prior art, it is not inventive, in the absence of an unexpected result, to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

15. Claims 13-21 and 160-168 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friend *et al.*, (1998) as applied to claims 1, 10-12, 22-26, 28-33, 45, 86, 87, 89, 90, 157-159, 169-173, 175-180, 265, and 280-282 above, further in view of Chee *et al.*, (US Patent No. 6,355,431B1, prior date: May 20, 1999).

The teachings of Friend *et al.*, have been summarized previously, *supra*.

Friend *et al.*, did not disclose to the limitations recited in claims 13-21 and 160-168.

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Chee *et al.*, teach the limitations recited in claims 13-21 and 160-168 (see columns 39 and 40).

Therefore, in the absence of unexpected results, it would have been obvious to one having ordinary skill in the art at the time the invention was made to have immobilized different amount of polynucleotide probes on an array as recited in claims 13-21 and 160-168 in view of patents of Friend *et al.*, and Chee *et al.*. One having ordinary skill in the art has been motivated to modify the method of Friend *et al.*, and combine above methods together because optimization of amount of immobilized polynucleotide probes on an array would have been obvious to one having ordinary skill in the art at the time the invention was made. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to optimization of amount of immobilized polynucleotide probes on an array. Note that where the general conditions of a claim are disclosed in the prior art, it is not inventive, in the absence of an unexpected result, to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Response to Arguments

In page 10, last paragraph bridging to page 14, first paragraph of applicant's remarks, applicant argues that: (1) "[F]riend teaches measuring the expression level of each of a plurality of genes rather than the expression levels of individual exons or multiexons in each of a plurality of genes." and (2) "[F]riend does not teach distinguishing among different variants of an exon."

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, as shown in the rejection under 112, second paragraph, it is

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unclear what mean “individual multiexons”. Second, as suggested by applicant, Friend *et al.*, teach measuring the expression level of each of a plurality of genes. Since multiexons is considered to have two or more exons and a cDNA often has two or more exons, a plurality of different multiexons are different cDNAs from different genes. On other word, each of a plurality of genes taught by Friend *et al.*, has a multiexon. Since, when the drug treatment had no effect, either directly or indirectly, on the relative abundance of a particular mRNA in a cell, the mRNA levels were equally prevalent in both cells while, when the drug treatment had an effect, either directly or indirectly, on the relative abundance of a particular mRNA in a cell, the ratio of the first fluorescence dye to the second fluorescence dyes either increased or decreased, the method taught by Friend *et al.*, measures the expression levels of a plurality of different multiexons in each of a plurality of different genes in the genome of an organism (ie., human) from which said cell sample is derived as recited in claim 1. Third, the examiner agrees with applicant that “[F]riend does not teach distinguishing among different variants of an exon.”. Since the phrase “wherein at least one gene in said plurality of different genes comprises an exon possibly having a plurality of different variants” indicates that said exon only has a possibility to have a plurality of different variants and said exon as recited in claim 1 can be read to not have a plurality of different variants, any limitation related to variants is not read into claim 1.

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Conclusion

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. No claim is allowed.

18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.


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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
June 27, 2003



ETHAN WHISENANT
PRIMARY EXAMINER